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Review

Metabolic syndrome and gastrointestinal diseases

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Metabolic syndrome is a cluster of metabolic abnormalities consisting essentially of obesity, especially abdominal obesity. Metabolic syndrome has been highlighted as a risk factor for cardiovascular and other chronic diseases. Obesity has been implicated in various gastrointestinal diseases such as gastroesophageal reflux diseases and colorectal cancer. Recently, abdominal obesity has been shown to be more important than obesity as expressed by an elevated body mass index as a causative factor for the development of these diseases. In addition to the mechanical effects of obesity, such as an increase in intra-abdominal pressure from large amounts of adipose tissue, substances that adipose tissues secrete, such as tumor necrosis factor-α, interleukin-6, leptin, and insulin-like growth factor-1, have been proposed to be pathogenic links to these diseases. In this review, we discuss the association of metabolic syndrome or the individual components of metabolic syndrome, focusing on obesity and abdominal obesity, with gastrointestinal diseases.

Key words: visceral obesity, adipokines, GERD, esophageal adenocarcinoma, colorectal cancer

Introduction

Metabolic syndrome is a cluster of metabolic abnormalities and is defined as the presence of three or more of the following factors: abdominal obesity (increased waist circumference [WC]), elevated triglycerides, low high-density lipoprotein (HDL) cholesterol, high blood pressure, and high fasting glucose.[1] Metabolic syndrome is a risk factor for cardiovascular and other chronic diseases. Metabolic syndrome has been drawing increasing attention, and abdominal obesity, especially visceral obesity (i.e., the accumulation of intra-abdominal fat), has been suggested to be the most clinically important obesity pattern. Sensitive measures for visceral obesity are WC and the waist-to hip ratio (WHR).[2] Although many studies of the relationship between obesity and several gastrointestinal diseases have been performed, literature on whether metabolic syndrome or abdominal obesity is a risk factor for gastrointestinal diseases is scant. We review the association of metabolic syndrome, or the individual components of metabolic syndrome, focusing on obesity and abdominal obesity, with gastrointestinal diseases.

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Gastroesophageal reflux disease, Barrett's esophagus, and esophageal adenocarcinoma

Gastroesophageal reflux disease (GERD) and obesity are two of the most common diseases in the United States and the Western world, and the incidence of both have been increasing rapidly. Recently, GERD was shown to affect around 20% of the U.S. population.[3] The prevalence of obesity [body mass index (BMI) $\geq 30\,kg/m^2$] is 30.5% in the U.S. population.[4] An association of symptoms of GERD with obesity has been reported,[5–10] and increases in symptoms of GERD are correlated with increases in BMI.[7,11] A cross-sectional population-based study from the United States by Lock et al.[6] that assessed risk factors for development of GERD symptoms identified a BMI $> 30\,kg/m^2$ as one risk factor [odds ratio (OR) 2.8; 95% confidence interval (CI), 1.7–4.5, compared with normal weight as defined by BMI $\leq 24\,kg/m^2$]. A cross-sectional population-based study from the United Kingdom showed that BMI was strongly and positively related to the frequency of symptoms of GERD.[5] The ORs for frequency of heartburn and acid regurgitation occurring

at least once a week in obese people compared with those of normal weight were 2.91 (95% CI, 2.07–4.08) and 2.23 (95% CI, 1.44–3.45), respectively. A population-based study from Germany also concluded that being overweight or obese was significantly associated with GERD symptoms.[12] On the other hand, a population-based study from Sweden found that the OR of people who had ever been obese or overweight (BMI ≥ 25 kg/m^2) during adulthood, compared with those who were never obese or overweight, having recurrent symptoms of GERD was 0.99 (95% CI, 0.66–1.47), and no association was found between reflux symptoms and BMI.[13]

In cross-sectional population-based studies, esophagogastroduodenoscopic examinations are not usually performed. Accordingly, participants with GERD, both nonerosive and erosive, Barrett's esophagus (BE), esophageal adenocarcinoma (EAC), or other diseases are all included. This diversity of diagnoses may influence the results. In studies in which endoscopic examination was performed in patients with GERD symptoms, the mean BMI is significantly higher among those with erosive GERD than among those with nonerosive GERD.[14,15] Van Oijen et al.[16] studied the association between BMI and symptoms of GERD in a population referred for upper gastrointestinal endoscopy and found that obesity and symptoms of GERD and also obesity and erosive GERD tended to be associated.[16] El-Serag et al.[11] studied whether an association between obesity and symptoms of GERD persists after adjusting for other known GERD risk factors such as age, sex, race, and smoking. A BMI > 30 kg/m^2 was associated with weekly heartburn or regurgitation (adjusted OR, 2.44; 95% CI, 1.27–4.67, compared with BMI < 25 kg/m^2). Both being overweight (BMI, 25–30 kg/m^2) and obesity were strong independent risk factors for erosive GERD.[11] However, Lundell et al.[17] reported that being massively overweight (BMI, 42.5 ± 5.2 kg/m^2) was not associated with abnormal acid reflux or erosive GERD. Nilsson et al.[18] reported a sex difference in the association between obesity and GERD symptoms. Although they found a positive dose–response association between higher BMI and GERD symptoms in both sexes, the association was stronger in female patients. Moreover, the degree of association differed between premenopausal and postmenopausal women, with the association stronger in premenopausal women. In a recent meta-analysis[19] of published data on the association between obesity and GERD, both being overweight (BMI, 25–30 kg/m^2) and obesity (BMI > 30 kg/m^2) were associated with a statistically significant increase in the risk for GERD symptoms, with ORs of 1.43 (95% CI, 1.158–1.774) and 1.94 (95% CI, 1.468–2.566), respectively, and being overweight or obese was a risk factor for erosive GERD (OR, 1.76; 95% CI, 1.156–2.677).

In accordance with empirical observations, weight loss is often recommended to reduce GERD symptoms. If there is a direct association between obesity and GERD, GERD symptoms or the degree of erosive GERD should be altered by weight change, and the findings of Nilsson et al.[18] support this hypothesis. They showed that the risk of reflux symptoms was increased (OR, 2.7; 95% CI, 2.3–3.2) among persons who gained more than 3.5 BMI units, compared with persons with stable BMI, while the risk of GERD symptoms was decreased (OR, 0.6; 95% CI, 0.4–0.9) among persons who lost more than 3.5 BMI units. However, data on the association of improvement of GERD symptoms with weight reduction are conflicting, with some reports showing improvement of GERD symptoms[20,21] and others showing no improvement.[22,23] The reason for the inconsistent results might be that the weight reduction was insufficient to effect an improvement or that irreversible changes at the esophagogastric junction, such as a hiatal hernia, may have followed an increase in BMI.

Assessment of the association of BMI and GERD involves many confounding factors. The association of obesity with GERD remains controversial, although much data indicate an increased risk of GERD in overweight or obese subjects. Recently, WC was reported to be associated with esophageal acid exposure to the same degree as BMI. After adjusting for WC, a BMI ≥ 30 kg/m^2 was no longer significantly associated with any measures of esophageal acid exposure. Consequently, abdominal obesity may be a more important causative factor for development of GERD symptoms than obesity as expressed by an elevated BMI.[24] More studies are needed to test this hypothesis.

The incidence of adenocarcinoma of the esophagus has been steadily increasing over the past three decades in the United States and other parts of the Western world, whereas that of squamous cell carcinoma of the esophagus has remained stable. Among white men, the incidence of EAC rose most prominently. Although a rising incidence has also been observed in white women and black men,[25] sex and race differences in the incidence still exist: the male:female incidence ratio is 8:1, and the white:black ratio is approximately 5:1.[25] The reasons for these differences are insufficiently understood.[26,27] GERD is known to be a risk factor for EAC,[28,29] and obesity is also thought to be a risk factor, because of the increasing incidence of EAC in parallel with the rapid increase in obese persons, coupled with the fact that obesity is known to be a risk factor for many cancers in Western countries.[30] This supposition is supported by several case–control studies.[31–34] A meta-analysis conducted by Hampel et al.[19] showed that both being overweight (BMI, 25–30 kg/m^2) and obesity (BMI > 30 kg/m^2) were associated with a statistically significant increase in the risk for EAC (OR, 1.52; 95% CI,

1.147–2.009 vs. OR, 2.78; 95% CI, 1.850–4.164, respectively).

Most EACs arise from BE, in which the esophageal squamous epithelium is replaced by a metaplastic columnar cell-lined epithelium. Progression from BE to adenocarcinoma is connected histologically by the metaplasia–dysplasia–carcinoma sequence.[35] GERD is a risk factor for BE,[28,29,36,37] and BE develops in approximately 10% of patients who have GERD.[38,39] The incidence of adenocarcinoma developing in patients with BE is 0.3%–1% yearly.[40–42] Accordingly, because obesity may be a risk factor for GERD, as discussed above, obesity may be indirectly associated with BE. Moreover, although what promotes the alteration of a benign esophageal epithelium to a malignant epithelium is unknown, obesity may directly modulate the susceptibility for progression to EAC. An epidemiological study has suggested that a high BMI might promote the progression of BE to EAC.[43] Although it has been reported that 60% of patients with EAC have a history of GERD symptoms, the remaining 40% have no prior reflux symptoms.[29] BE is sometimes detected in asymptomatic persons,[44] and some patients with adenocarcinoma following BE have no GERD symptoms.[45,46] Risk factors for BE other than GERD are poorly understood, and identifying such risk factors for BE would be very useful for detection of asymptomatic BE and EAC. Studies of whether obesity is a risk factor for BE are few. Stein et al.[47] reported that obese patients are at greater risk for BE, whereas Chak et al.[48] showed that obesity alone was not associated with the presence of BE, but that the duration of obesity was associated with BE. Smith et al.[49] showed that obesity markedly increased the risk of BE in subjects with GERD symptoms but that obesity alone did not. Whether obesity is an independent risk factor for BE remains controversial. The pattern of obesity has been known to influence the risk for several diseases. The risk for persons with visceral obesity of developing insulin resistance syndrome and cardiovascular disease is higher than that for persons with peripheral obesity. El-Serag et al.[50] examined the effect of the pattern of obesity on the development of BE and showed that both BMI and the surface areas of visceral adipose tissue (VAT), measured by computed tomography scan, were significantly associated with an increased risk of BE. VAT remained independently associated with BE after adjusting for BMI, while the significant association of BMI with BE was abolished after adjusting for VAT. A higher WHR was significantly related to increasing risks of aneuploidy, loss of heterozygosity at chromosome 17p (17pLOH), and 9pLOH, which were demonstrated or suspected to be predictive of subsequent cancer development from BE, whereas a higher BMI was not.[51] Consequently, visceral obesity may be important in increasing the risk of BE and promoting the progression of BE to EAC. Visceral obesity is more common in men, thus partly explaining the sex difference in EAC (male predominance).

Increased transient lower esophageal sphincter (LES) relaxation, hypotensive LES tone, and hiatal hernia are main causative factors of GERD.[52–55] In addition, abnormal esophageal and gastric motility,[56,57] a salivary secretion disorder,[58] or impaired mucosal defense mechanisms[59] can modulate the degree of injury from acid reflux. Several mechanisms by which obesity may cause GERD, BE, and EAC are proposed (Fig. 1). Obesity

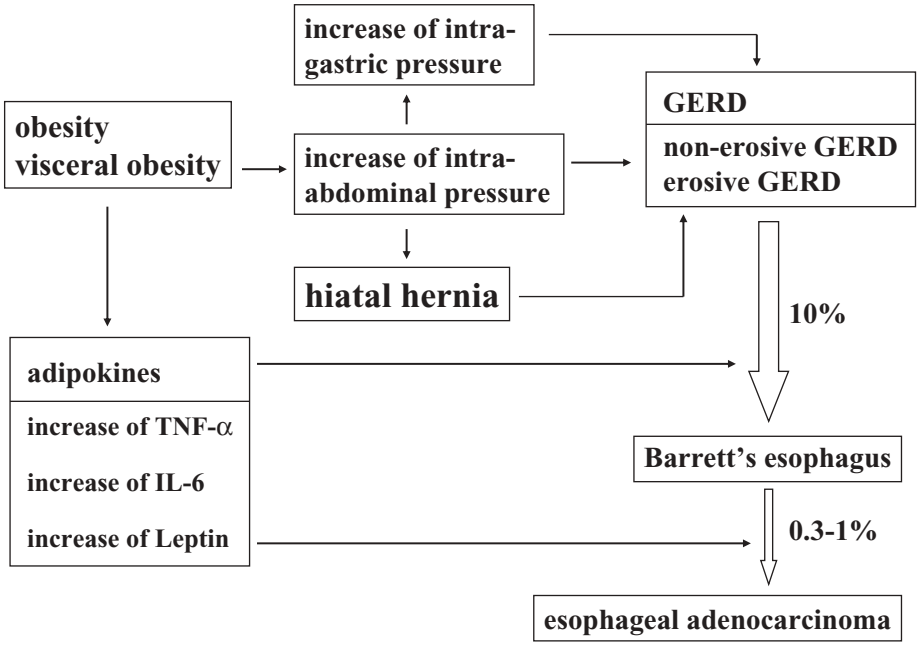

Fig. 1. Current hypothesis regarding the mechanisms by which obesity may cause gastroesophageal reflux disease (*GERD*), Barrett's esophagus, and esophageal adenocarcinoma. *Arrows* represent a positive influence. *Open arrows* labeled 10% and 0.3–1% indicate the proportions of patients with Barrett's esophagus and esophageal adenocarcinoma, respectively. *TNF-α*, tumor necrosis factor-α; *IL-6*, interleukin-6

may increase intra-abdominal pressure, leading to increased intragastric pressure and consequently to an increased gastroesophageal pressure gradient inducing LES relaxation.[60] Moreover, an increase in intra-abdominal pressure by obesity can result in the development of a hiatal hernia that displaces the LES.[61] Therefore, obesity is a significant independent risk factor for hiatal hernia,[21] and the size of the hernia is predictive of the severity of the esophagitis and affects LES pressure.[62,63] Recently, although both BMI and WC are associated with both intragastric pressure and the gastroesophageal pressure gradient, WC has been reported to have a stronger association than BMI.[24] Accordingly, visceral fat deposition may be an important causative factor of GERD. As the positive association between BMI and GERD symptoms is stronger among premenopausal than among postmenopausal women,[18] estrogen may play a role in the association.

Additionally, adipose tissues, especially visceral adipose tissues, which are metabolically active, are strongly associated with increasing serum levels of adipokines, including interleukin (IL)-6 and tumor necrosis factor (TNF)-α,[64] which may play a role in GERD or consequent carcinogenesis. Leptin is secreted predominantly by adipose tissues, and serum levels increase in proportion to body fat mass.[65] Leptin has been shown to stimulate cell proliferation and inhibit apoptosis in Barrett's-derived EAC cells.[66] The characteristics of increased proliferation and reduced apoptosis, which are often noted in BE, are important in the progression to cancer because they promote the accumulation and persistence of genetic abnormalities.

Adenocarcinoma of gastric cardia and colorectal cancer

The incidence of adenocarcinoma located in the cardia has increased.[25,67] Several studies that have examined the association between obesity and the risk of cardia adenocarcinoma have reported conflicting results.[33,68,69] Some reported an association with increased risk of cardia adenocarcinoma while others found either no association or a negative one. A meta-analysis in 2006[70] indicated that the overall association of high BMI with cardia adenocarcinoma was heterogeneous, and that a high BMI was weakly associated with the risk of cardia adenocarcinoma in limited populations from the United States or Europe (OR 0.5; 95%CI, 1.3–1.8); Chinese studies, however, did not show such an association. A meta-analysis in 2005[19] similarly reported a heterogeneous overall association. Accordingly, the association between obesity and the risk of cardia adenocarcinoma remains controversial.

Colorectal cancer is the second-leading cause of cancer death in the United States, accounting for approximately 52 000 deaths annually.[71] The precise causes of colorectal cancer remain unknown, although family history and several dietary and lifestyle factors have been proposed to increase the risk.[72,73] Several studies have shown that increased BMI is associated with an increased risk of colorectal cancer, especially in men.[74–78] Moreover, Giovannucci et al.[78] demonstrated that high values of WC and WHR were strong risk factors for colorectal cancers. Relative risk of WHR $\geq$ 0.99 compared with WHR < 0.90 was 3.41 (95% CI, 1.52–7.66), and that of WC $\geq$ 43 inches (about 109 cm) compared with WC < 35 inches (about 89 cm) was 2.56 (95% CI, 1.33–4.96) for colorectal cancer. Schoen et al.[79] also reported that higher WC measurements were significantly associated with colorectal cancer. As visceral obesity is more common in men, the fact that the association is observed more strongly in men than in women suggests that visceral obesity may mediate between BMI and the increased risk of colorectal cancer. A malignant disease often influences the body weight of the host, so anthropometric measurements are of doubtful significance in patients with established colorectal cancer. For this reason, the association between colorectal adenomas recognized as precancerous lesions of the colon and rectum and obesity has been investigated. Giovannucci et al.[78] found that BMI was not significantly associated with an increased risk of distal colon adenoma irrespective of size, while WC and WHR were strong risk factors for large distal colon adenomas with diameter $\geq$ 1 cm but were unrelated to small adenomas with diameter < 1 cm. The association of WC with an increased risk of cancer has been reported to be slightly stronger for distal colon cancer.[78] The degree of influence may differ among regions of the colon when obesity plays a role as a risk factor for colon cancer. Being overweight in adolescence in addition to being overweight in adulthood has also been suggested to be an important factor in colorectal cancer carcinogenesis.[80,81] The association between obesity and the risk of colorectal cancer cannot be easily explored because many confounding factors exist. Thus, further subanalyses are needed.

The association between risks of colorectal cancer and several components of metabolic syndrome has been studied. Type 2 diabetes increases the risk of colorectal cancer 1.3- to 1.6-fold, with the risk of proximal colon cancer being greater.[82] The role of insulin in the association between diabetes mellitus and increased risk of colorectal cancer is unclear. Although Yoshida et al.[83] reported that serum insulin levels directly correlate with the presence of adenoma and hyperplastic polyps in the proximal colon, the association between high levels of insulin and increased risk of colorectal

cancer has not yet been elucidated.[84,85] Several researchers investigated the association between triglycerides and HDL cholesterol and increased risk of colorectal cancer, but the results are conflicting,[74,79,81,86] so further studies are needed. Ahmed et al.[87] examined whether metabolic syndrome was a risk factor for colorectal cancer. Metabolic syndrome that fulfilled diagnostic criteria[1] was positively associated with age-adjusted and sex-adjusted colorectal cancer development, and a dose–response association between colorectal cancer development and the number of metabolic syndrome components was noted (P for trend = 0.006). Additionally, analysis of the sex distribution revealed that metabolic syndrome was a risk factor for development of colorectal cancer in men but not in women. Wang et al.[88] reported that the OR of the development of colorectal adenoma increased incrementally with the number of metabolic syndrome components present, compared with polyp-free patients.

Obesity is an important risk factor for colorectal cancer. Figure 2 outlines the current hypothesis regarding the linkage of obesity with colorectal cancer. Adipose tissue, especially VAT, is not merely a fat-storing tissue but a metabolically active organ secreting many adipokines, such as TNF-α, IL-6, and adiponectin, which are proteins that are synthesized and secreted by adipocytes. Adipose tissue is also the source of growth factors such as insulin-like growth factor-1 (IGF-1), which is produced in the liver. These substances, including TNF-α, IL-6, and adiponectin, secreted from adipose tissue, are known to cause insulin resistance syndrome.[64] Accordingly, obesity is strongly associated with the state of insulin resistance, in which levels of insulin and IGF-1 are elevated. Insulin is an important growth factor for colonic mucosal cells and colonic carcinoma cells in vitro,[89–91] and IGF-1 inhibits apoptosis and promotes cell cycle progression, leading to development of cancer.[92,93] Insulin is known to be anti-inflammatory, and anti-inflammatory agents have been shown to reduce the risk of colorectal neoplasm;[94,95] therefore, the link between hyperinsulinemia and colorectal neoplasm is unclear. Moreover, obesity has been suggested to be associated with tissue inflammation, which is mediated by adipose tissue. It is speculated that this subclinical inflammation is associated with development of colorectal cancer[96] as long-standing inflammation causes colorectal cancer in patients with ulcerative colitis.[97]

Conclusions

Obesity, especially visceral obesity, appears to be involved in several gastrointestinal diseases. Visceral obesity is the core of metabolic syndrome, so metabolic syndrome can be supposed to be associated with gastrointestinal diseases. Associations between gastrointestinal disease and individual components of metabolic syndrome other than obesity have not been studied extensively. Each component of metabolic syndrome may interact to increase the risk of gastrointestinal diseases, and, accordingly, a cluster of metabolic abnormalities that fulfill diagnostic criteria of metabolic syndrome[1] may raise the risk of gastrointestinal diseases by a larger increment than an individual metabolic abnormality. However, there have not been sufficient studies to prove this hypothesis, and further studies are needed to clarify these associations. Moreover, ethnic differences are known to exist in genetic background, such as a suscep-

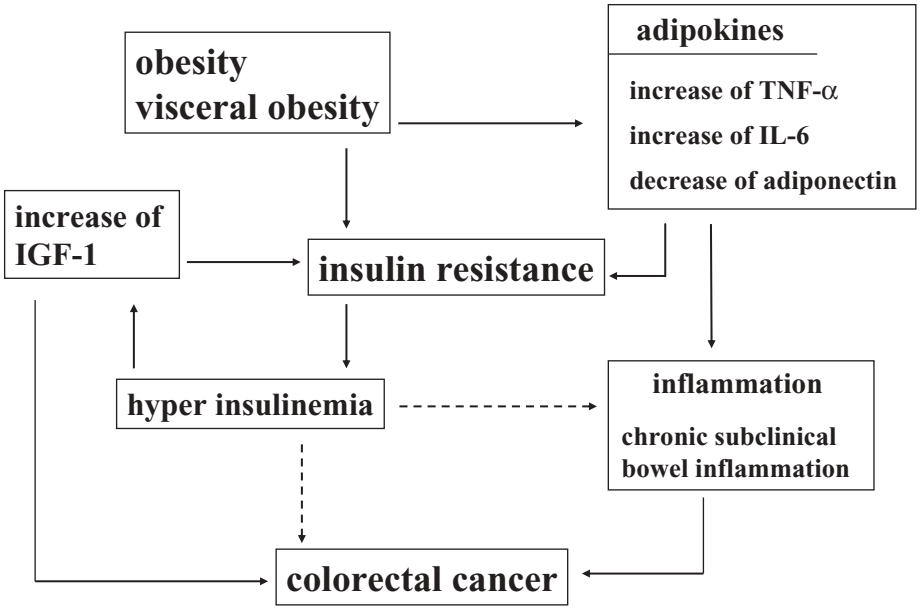

Fig. 2. Current hypothesis regarding the linkage of obesity with colorectal cancer. *Arrows* represent a positive influence. Possible influence is represented by *dotted arrows*. *IGF-1*, insulin-like growth factor-1

tibility of Japanese people to type 2 diabetes.[98] Reports from Japan, which is ethnically fairly homogeneous, would be of great interest.

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